REMARKS

THE CLAIM AMENDMENTS

Applicants have amended claims 1 and 70-72; canceled claims 5, 33, 63 and 64; and added new claim 74. Applicants had previously canceled claims 3-4, 9-32, 34-62, 67-69 and 73. After entry of this amendment, claims 1, 2, 6-8, 65, 66, 70-72 and 74 will be pending in this application.

Applicants have amended claim 1 to delete "striatum" and to positively recite that the administration is outside of the striatum. Claim 1 and the claims that depend from it now refer to an administration site outside of the ventricles and outside of the striatum and to a location selected from the pallidum, septum, cortex, external capsule, internal capsule, substantia nigra-ventral tegmentum, and at or adjacent to an ependymal or subependymal zone. This amendment is supported, for example, by former claims 1 and 33.

Applicants have also amended claim 70, and the claims that depend from it, to recite administration "outside of the striatum". This amendment is supported, for example, by former claim 70.

Applicants have also amended claims 71 and 72 to correspond to the cancellation of claims 33 and 63.

Applicants have added new claim 74, which depends from any one of claims 1, 65, 66 or 70. It is supported by former claim 64 (now canceled). It is also supported in the application, as filed. See, e.g., Example 2 at pages 40-67.

Applicants' cancellation of subject matter by amendment herein is specifically without waiver of applicants' rights to file divisional or continuing applications directed to this subject matter and claiming the benefit of and priority to this application.

THE FEBRUARY 15, 2011 FINAL OFFICE ACTION

35 U.S.C 119(e): Priority

Applicants thank the Examiner for considering Applicant's December 2, 2010 Amendment and Response, and for granting the priority date of August 4, 1997 to claims 1, 2, 5 (now canceled), 6-8, 33 (now canceled), 63-64 (both canceled), 65, 66 and 70-72.

New claim 74 depends from any one of claims 1, 65, 66 or 70. Therefore, claim 74 is also entitled to an effective filing date of August 4, 1997. Applicants request that the Examiner grant such priority to new claim 74.

Claim Objections

(1) Claim 33

The Examiner, citing MPEP §706.03(k), has objected to former claim 33 as allegedly being a substantial duplicate of claim 1. (See Office Action, page 2.)

In the Office Action, the Examiner has not indicated that either of claim 1 or claim 33 is allowable. Thus, this objection would seem to be premature. Moreover, the claims are not identical. Claim 1 recites that the administration of the TGF-α polypeptide effects migration of a neural progenitor cell or a progeny to a site of damage or lesion in the CNS. By contrast, claim 33 recites that the administration of the TGF-α polypeptide attracts the neural progenitor cell or a progeny to the site of damage or lesion. Nonetheless, solely to advance the prosecution of the present application, applicants have canceled claim 33, thus, rendering this objection moot.

(2) Claim 70

The Examiner has objected to former claim 70 for allegedly having improper punctuation. In particular, the Examiner has pointed out that there are two periods at the end of the claim. Applicants have deleted one period, thus, obviating the objection.

35 U.S.C. §112: Second Paragraph

(1) Claim 2

The Examiner has rejected claim 2 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. According to the Examiner, claim 2 is "missing active method steps leading to the stimulation of differentiation of neural progenitor cell" (see Office Action, page 3). The Examiner further contends that "absent such steps the claim appears to merely encompass a result of the administration step and fail to distinguish from the subject matter of the parent claim" (see Office Action, page 3). Applicants disagree. Claim 2 is not indefinite for at least the following reasons.

First, claim 2 depends from claim 1, where the active step of the method is clearly set forth: administration of the neural TGF-α polypeptide composition. Therefore, claim 2 is not missing an active method step.

Second, the recitation in claim 2: "wherein the administration further stimulates differentiation of the neural progenitor cell or a progeny thereof" is a result of that active step. In particular, claim 1 recites that administration of the TGF-α polypeptide effects migration of neural progenitor cells to a site of CNS damage or lesion. Claim 2 recites that the administration also effects differentiation of the cells. Applicants have clearly described such differentiation in the application, as filed, and how to detect/assay the differentiated neurons. See, e.g., page 31, line 14 to page 33, line 28 and Example 3. For the above reasons, claim 2 is not indefinite. Applicants request that the Examiner reconsider and withdraw the rejection.

(2) Claim 8

The Examiner has rejected claim 8 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. According to the Examiner, "spinal nerve root origins" as recited in claim 8 refers to dorsal or ventral roots of the spinal cord. The Examiner contends that claim 1, from which claim 8 depends, recites a Markush group of tissues, i.e. "the group consisting of the pallidum, septum, cortex, external capsule, internal capsule, substantia nigra-ventral tegmentum, and at or adjacent to an ependymal or subependymal

zone", none of which is within the spinal cord. The Examiner then argues that there is, at least, a lack of antecedent basis for the term "spinal nerve root origins" in claim 1. Applicants disagree.

The recitation "spinal nerve root origins" in claim 8 has antecedent basis in its parent claim (i.e., claim 1). The Markush group recited in claim 1, to which the Examiner points, refers to possible sites for administering TGF-α, not the CNS site of damage or lesion. By contrast, the "spinal nerve root origins" recited in claim 8 are the CNS tissue in which the damage or lesion is located. This difference – site of administration vs. location of CNS damage – is clearly indicated in claim 1 (from which claim 8 depends). See, e.g., claim 1, lines 1-3. It is common knowledge in the field that CNS tissue is any tissue located within CNS, including the spinal cord. Thus, the recitation in claim 8 that the CNS tissue, in which the site of damage/lesion is present, is spinal nerve root origins has antecedent basis in its parent claim (claim 1). For all the above reasons, applicants request that the Examiner reconsider and withdraw the rejection.

35 U.S.C. §102(b): Anticipation

The Examiner has rejected former claims 1, 5-7, 33, 63-65 and 70 as allegedly lacking novelty under 35 U.S.C. § 102(b) over Loughlin (Loughlin et al., "Transforming Growth Factor Alpha: A Potential Role in the Efficacy of Intrastriatal Transplants", 1992, Soc. NeuroSci. Abs.). According to the Examiner, Loughlin reports "a method comprising administering TGF-alpha by intrastriatal infusion for 'over a two week period' to animals that have a 6-OHDA lesion" and that animals receiving the TGF-alpha infusion exhibited "significantly decreased rotation behavior" (see Office Action, page 4). The Examiner contends that, although Loughlin is silent with respect to "attracting neural progenitor cells" or "effect[ing] migration of the neural progenitor cell", Loughlin allegedly recites the active administration of TGF-α step as required by the claimed method. The Examiner then argues that Loughlin's method, therefore, inherently leads to the migration or attraction of neural progenitor cells, as recited in the rejected claims. On those alleged

bases, the Examiner argues that the method of Loughlin is identical or substantially identical to the claimed method, and that "the burden of proof rests upon the Applicant to demonstrate that the prior art does not necessarily or inherently possess the characteristics of Applicant's claimed product" (see Office Action, page 6). Applicants traverse.

As set forth above, applicants have canceled claims 5, 33, 63 and 64, thus, obviating the novelty rejection as to those claims. As discussed in detail below, claims 1, 6, 7, 65 and 70 are novel over Loughlin.

The Loughlin Abstract is directed to testing a hypothesis that TGF-α might play a role in the efficacy of transplants. Loughlin treated 6-OHDA lesioned animals with intrastriatal infusions of TGF-α over a two week period. While Loughlin reported an improvement in rotational behavior, it acknowledged that it was not known whether the observed improvement reflected regeneration of dopaminergic afferents or other compensatory changes. Loughlin's conclusion in the context of TGF-α's role in transplants was also speculation: it is possible that the efficacious effects of transplants in Parkinson's disease are mediated through TGF-α.

In a 1994 book chapter (of record), Loughlin said much the same thing. Like the 1992 Abstract, the 1994 book chapter was directed at an investigation of the possible role of trophic factors in the efficacy of intrastriatal transplants in Parkinson's disease (page 205). In particular, Loughlin examined the role of two families of growth factors – fibroblast growth factors and growth factors which bind to the EGF receptor, including TGF-α – in transducing the efficacy of the transplants (page 206).

Loughlin reported that transplants led to an increase of TGF-α precursor-like immunoreactivity (TGFαP-IR) and a corresponding increase in TGF-α mRNA (page 208). Loughlin then speculated that astrocytes were the source of the TGF-α (page 208).

To test the hypothesis that TGF-α might play a role in the ameliorating effect of transplants, Loughlin treated 6-OHDA lesioned animals with intrastriatal infusions of TGF-α (page 209). Loughlin then reported that the infusions caused an increase in TGFαP-IR and TGF-α mRNA, just like the transplants had (page 209). She also observed, as she

reported in the 1992 Abstract, decreased rotational behavior (page 209). Loughlin concluded that the brain is capable of increasing the population of TGF-α synthesizing astrocytes in the absence of transplants (page 209). Loughlin also acknowledged that the mechanism by which TGF-α infusions improved motor behavior in 6-OHDA lesioned animals was unknown, speculating that they might involve regeneration of dopaminergic afferents, increased efficacy of remaining dopaminergic terminals, normalization of dopamine receptor populations or compensatory changes in other neurochamical systems (page 209). Loughlin then concluded that it was possible that the efficacious effects of transplants were mediated directly by TGF-α (page 209).

The rejected claims recite methods of attracting a neural progenitor cell or its progeny to the site of CNS damage or lesion (claim 1), and stimulating differentiation of the cells (claim 2), both are evidenced by an amelioration of behavioral deficits attributable to the damage or lesion. As demonstrated above, Loughlin provides no such teaching. On that basis alone, Loughlin does not render the claims unpatentable.

Nonetheless to advance prosecution, applicants have amended claim 1 to delete "striatum" and to positively recite that the TGF-α polypeptide administration is outside of the striatum. Claim 1 and the claims that depend from it (including claims 6 and 7), therefore, no longer recite intrastriatal administration. They now refer to a TGF-α administration site outside of the ventricles and the striatum and being selected from the pallidum, septum, cortex, external capsule, internal capsule, substantia nigra-ventral tegmentum, and at or adjacent to an ependymal or subependymal zone. As demonstrated above, Loughlin does not teach administering TGF-α to any of these sites. For this reason also, claim 1 and the claims that depend from it (including claims 6 and 7) are novel over Loughlin.

Claim 65 is also novel over Loughlin. Claim 65 refers to a method comprising administering to the subject a TGF-α peptide, where "the administration is for a period of at least about sixteen days". Loughlin does not teach an administration for such a time period. In fact, Loughlin refers only to a method where TGF-α was administered "over a

two week period", i.e. 14 days. Nowhere in Loughlin is it taught that the TGF-α should be administered for more than 14 days. For this reason, claim 65 and the claims that depend from it are novel over Loughlin.

Applicants have amended claim 70 to recite "wherein said administration is outside of ventricles and outside of the striatum". By contrast, Loughlin only refers to the intrastriatal administration, which is specifically excluded from claim 70. For this reason, claim 70 and the claims that depend from it are novel over Loughlin.

In light of the above, applicants request that the Examiner reconsider and withdraw the novelty rejection as to claims 1, 6, 7, 65 and 70.

35 U.S.C. §103(a): Obviousness

Claims 1, 2, 5-8, 33, 63-66 and 70-72 stand rejected as allegedly obvious under 35 U.S.C. § 103 over Loughlin (Loughlin et al., Soc. Neurosci. Abs. 1992) in view of Weiss (US patent 5,980,885). According to the Examiner, Loughlin "teaches that it was known in the prior art that administration of TGF-alpha by intrastriatal infusion for a two week period provided therapeutic treatment to subjects having a CNS lesion, and that efficacy could be assessed by behavioral effects" (see Office Action, page 7). The Examiner then points to Weiss and contends that (1) Weiss is "enabled for methods comprising TGF-α"; (2) Weiss "contemplates use of the method at the site of damage or lesion where promotion of proliferation and differentiation of neural stem cell progeny would effect treatment of neurological injuries or disease"; and (3) Weiss "teaches that the invention provides a means for generating large numbers of undifferentiated and differentiated neural cells in vivo, arising from the ependymal zone, as required by instant claim 72 (Column 13 lines 21-41)" (see Office Action, pages 7-8). On those alleged bases, the Examiner maintains that the claimed method as recited in former claims 1, 2, 5-8, 33, 63-66 and 70-72 is allegedly obvious. Applicants traverse.

Applicants have canceled claims 5, 33, 63 and 64, thus, obviating the rejection as to those claims. As discussed in detail below, pending claims 1, 65, 66, 70, and the claims that depend from them, are not obvious over the combination of Loughlin and Weiss.

(1) Loughlin

As demonstrated above, the pending claims refer to methods for attracting a neural progenitor cell, or a progeny thereof, to a site of damage or lesion in a CNS tissue. The methods comprise administrating TGF-α, where:

i. the administration is outside of ventricles, outside of the striatum, and to a location selected from the group consisting of the pallidum, septum, cortex, external capsule, internal capsule, substantia nigra-ventral tegmentum, and at or adjacent to an ependymal or subependymal zone, which group excludes Loughlin's intrastriatal administration and Weiss' ventricle administration (see claim 1);

ii. the administration is outside of ventricles and to a location selected from the group consisting of the striatum, pallidum, septum, cortex, external capsule, internal capsule, substantia nigra-ventral tegmentum, and at or adjacent to an ependymal or subependymal zone, and the administration is for a period of at least sixteen days, which excludes Loughlin's "over a two week period" administration and excludes Weiss' ventricle administration (see claim 65);

iii. the administration is outside of ventricles and to a location selected from the group consisting of the striatum, pallidum, septum, cortex, external capsule, internal capsule, substantia nigra-ventral tegmentum, and at or adjacent to an ependymal or subependymal zone, and the administration is initiated weeks after the occurrence of the damage or lesion, which excludes Loughlin's administration immediately after induction of the lesion and excludes Weiss' ventricle administration (see claim 66); or

iv. the administration is outside of ventricles and outside of the striatum, which excludes Loughlin's intrastriatal administration and excludes Weiss' ventricle administration (see claim 70).

As discussed above, claims 1, 65, 70 and the claims that depend from them are novel over Loughlin. The Examiner herself acknowledges that claim 66 is novel over Loughlin. She did not reject that claim for alleged lack of novelty. Furthermore, none of these claims is obvious over any combination of Loughlin and Weiss.

(a) Claims 1 and 70

The methods of claims 1 and 70 comprise administration of TGF-α to the CNS and outside of the ventricles and outside of the striatum. By contrast, as demonstrated above Loughlin does not teach such administration. Indeed, there is no suggestion in Loughlin that the TGF-α should be administered outside of the striatum. And, there is no suggestion that the TGF-α would have any beneficial efforts, even in the context of transplants, when administered outside of the striatum.

The claimed methods (claims 1 and 70) also require that the administration effects migration of neural progenitor cells or their progeny to a site of damage or lesion in the CNS as evidenced by an amelioration of behavioral effects attributable to the damage or lesion. By contrast, as demonstrated above, Loughlin's experiments were carried out solely to test the hypothesis that "TGF-α might play a role in the efficacy of transplants". Loughlin's conclusion of the experiments was "it is possible". Based on the reported studies, Loughlin acknowledged that the method by which TGF- α improved motor behavior was unknown. At best, Loughlin speculated about a number of possible mechanisms (see *supra*, pages 11-12). Indeed, as the Examiner has conceded, the Loughlin Abstract is completely silent regarding attracting (or effecting migration of) neural progenitor cells or their progeny to a site of CNS damage/lesion. And, what Loughlin suggested in the 1994 book chapter was that a population of TH-IR fibers was localized in the region surrounding the TGF-α infusions. Loughlin then questioned whether such fibers represented regenerating afferents or the sprouting of other TH-IR fibers. Therefore, a skilled artisan reading Loughlin would have had no reason to expect that administering TGF-α into striatum of a lesioned subject, as Loughlin does (and certainly not into other parts of the CNS), would attract (or effect the migration of) the neural

progenitor cells and their progeny to the site of a CNS lesion or damage so as to ameliorate the behavioral deficits attributable to the damage or lesion.

(b) Claim 65

Claim 65, like claims 1 and 70, recites that the TGF-α polypeptide effects migration of neural progenitor cells or their progeny to a site of damage or lesion in the CNS. As a consequence, claim 65 is not obvious over Loughlin for the same reasons that claims 1 and 70 are not obvious over Loughlin.

In addition, claim 65 recites that the administration is for a period of at least 16 days. As we demonstrated above when addressing novelty, Loughlin infused the TGF-α over a period of two weeks. Loughlin does not suggest that longer administration would be useful or effectious. By contrast, the pending application reports that the migration of the neural progenitor cells in the striatal ridge increased dramatically between 12 and 16 days. At 12 days it was "as much as 400 μm" from the ventricle wall. But, by 16 days it was 5x further ("up to 2mm") from the wall. See, e.g., page 55, line 15 to page 56, line 2.

For both reasons, claim 65 is not obvious.

(c) Claim 66

Claim 66, like claims 1 and 70, recites that the TGF-α polypeptide effects migration of neural progenitor cells or their progeny to a sit of damage or lesion in the CNS. As a consequence, claim 66 is not obvious over Loughlin on this basis for the same reasons that claims 1 and 70 are not obvious over Loughlin.

In addition, claim 66 recites that the TGF-α administration is done weeks after the occurrence of the CNS damage or lesion. By contrast, Loughlin reports that the TGF-α was infused simultaneously or very shortly after the 6-OHDA lesion. Nowhere does Loughlin suggest that the TGF-α administration could be done, much less be effective, weeks after the injury. In clinical application, this time difference in injury vs. administration is important. A patient suffering from a CNS lesion or damage will rarely, if ever, present for treatment concurrently with the occurrence of the lesion or damage. Therefore, for these reasons, claim 66 is not obvious over Loughlin.

(2) Weiss

Weiss does not remedy any of the deficiencies of Loughlin in the context of the Examiner's obviousness rejections. Weiss does not teach or suggest that administration of TGF-α at a location outside of the ventricles would induce sufficient cell migration, proliferation and differentiation to achieve the amelioration of behavioral deficits attributed to the injury or lesion.

In particular, as discussed in Applicants' December 2, 2010 Response to the June 2, 2010 non-final Office Action, although TGF-α is mentioned in Weiss, Weiss places no particular emphasis on TGF-α (e.g., col. 15, line 60 – col. 16, line 23; col. 19, lines 29-43; and col. 25, lines 41-55) or its administration outside of the ventricles (e.g., col. 25, line 41-col. 26, line 15). Instead, Weiss' specific examples of administration of growth factors *in vivo* use only FGF, EGF, or a combination of EGF and FGF, and administering them only into the ventricles (i.e., "ICV"). *See* Weiss at col. 46-49, Examples 27-31; Weiss at col. 17, lines 9-14. For these reasons, Weiss does not remedy Loughlin's failure to suggest administration of TGF-α at a non-ventricle location outside of the striatum, (i.e., claims 1 and 70).

As applicants have also previously discussed and evidenced, none of Weiss's methods led to significant proliferation or migration of cells or any improvement in behavior or function. In fact, Weiss's methods only lead to a proliferation of 350 cells per brain (see, e.g., Weiss at col. 47, lines 40-43), a number far too low to have any biological effects. This result was also confirmed by Dr. Fallon's experiments and the work of others (such as Reynolds and Kuhn), which applicants discussed in detail in Applicants' December 2, 2010 Response to June 2, 2010 non-final Office Action, as well as in Fallon I and II Declarations. For these reasons also, Weiss does not remedy Loughlin's failure to suggest that TGF-α effects of migration of neural progenitor cells and their progeny to a site of injury or lesion in the CNS (claims 1, 65, 66 and 70).

The skilled worker, with Loughlin and Weiss in hand, also would have had no reason to expect that administration of TGF-α outside the ventricles for over 16 days or

weeks after the occurrence of the injury, as recited in pending claims 65 and 66, would result in cell proliferation, migration, differentiation and the amelioration of behavioral effects attributable to the CNS injury.

For all the above reasons, Loughlin and Weiss, either alone or in combination, do not make any of the claimed methods obvious. Therefore, amended claims 1, 45, 65, 66, 70, and the claims that depend from them, are not obvious over Loughlin and Weiss, either alone or in combination. Applicants request that the Examiner reconsider and withdraw the rejection.

Double Patenting

The Examiner has maintained the double patenting rejection of claims 1, 5, 6, 33, 63, 65 and 70-72 under the judicially created doctrine of obviousness-type double patenting over formerly co-pending United States patent application 09/129,028 (now US patent 7,790,669) and 10/167,384 (now US patent 7,795,202).

Applicants have cancelled claims 5, 33 and 63, thus obviating the above rejections as to those claims.

In the pending Final Office Action, the Examiner has not indicated any allowable subject matter. Therefore, applicants continue to request that the above double patenting rejections, as to any of the remaining claims, be held in abeyance until allowable subject matter is found in the instant application. Depending on the claims identified as allowable, applicant will then respond to the obviousness-type double patenting rejection in the appropriate way, *i.e.*, by argument or by the filing of the appropriate Terminal Disclaimer.

Related Applications

Applicants call the Examiner's attention to the entire prosecution of the following applications:

Application No.	Filing Date	Status	Atty. Dkt. No.
09/129,028	08/04/1998	Issued (US Patent 7,790,669)	108091-0002-101
09/920,085	07/31/2001	Abandoned	n/a
10/167,384	06/10/2002	Issued (US Patent 7,795,202)	108091-0002-102
12/869,468	08/26/2010	Pending	108091-0002-105
12/869,486	08/26/2010	Pending	108091-0002-106

U.S. Patent Application 09/129,028 ('028 application), filed August 4, 1998 (now U.S. Patent 7,790,669), claims benefit and priority from U.S. Provisional Patent Application 60/055,383, filed August 4, 1997. The present application is a continuation-in-part (CIP) of the '028 application.

U.S. Patent Application 09/920,085, filed July 31, 2001 (now abandoned) is a continuation of the '028 application.

U.S. Patent Application 12/869,468, filed August 26, 2010, also is a continuation of the '028 application.

U.S. Patent Application 10/167,384 ('384 application), filed June 10, 2002 (now U.S. Patent 7,795,202) is a continuation-in-part (CIP) of the '028 application, which claims benefit and priority from U.S. Provisional Patent Application 60/055,383, filed August 4, 1997. The '384 application also claims the benefit of U.S. Provisional Patent Application No. 60/328,725, filed Oct. 11, 2001, and U.S. Provisional Patent Application No. 60/297,518, filed Jun. 11, 2001.

U.S. Patent Application 12/869,486, filed August 26, 2010, is a continuation of the '384 application.

CONCLUSION

In view of the amended claims and the above arguments, applicants request allowance of the amended claims. The Examiner is invited to telephone the undersigned at (212) 596-9034 for any reason to advance the prosecution of the application.

Respectfully submitted,

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